REMARKS

Claims 1-5, 8, 11-17, 22-24 and 27 were pending prior to entering the amendments.

The Amendments

Claims 2 and 8 are cancelled.

Claims 23 and 27 are amended to clarify the claim language.

No new matter is added in any of the amendments. The Examiner is requested to enter the amendment and reconsider the application.

The Present Invention

Metaplasia

The dictionary definition of metaplasia is abnormal replacement of cells of one type by cells of another (see Merriam Webster's Collegiate Dictionary, 10th Edition, 1997, page 731, copy attached). The cervix is located between the vagina and the uterus. The vaginal epithelium is squamous epithelium, and the uterine epithelium is columnar epithelium. The cells in the cervical area can undergo the transformation of one type of mature differentiated cell type into another mature differentiated cell type (squamous to columnar, or columnar to squamous). In this stage of cellular differentiation, the cells are called metaplastic cells. The morphology of metaplastic cells resembles immature cells and it is not dissimilar from the morphology of dysplastic cells. Metaplasia is not considered carcinogenesis and it is important to discriminate metaplasia from pre-cancerous or cancerous lesions.

The present invention identifies the problem that about 30% of metaplastic cells show some immunoreactivity with $p16^{INK4a}$ specific antibodies, and could lead to false-positive results in mataplasia cells (page 1, lines 20-21). This unique problem exists only in the cytological (cell-type) testing, and is not a problem in histological (tissue-type) testing. A positive result of p16 of metaplastic cells in histological testing is not a problem because the availability of the tissue-based morphological information. However, in cytological testing such as by Pap smear, the tissue information does not exist and thus a positive result of p16 in metaplastic cells is indeed a problem for diagnosis.

None of the cited prior art has either identified the problem, let alone provided a solution.

The Present Claims

The present invention provides a method for discriminating $p16^{INK4a}$ overexpressing metaplasias from $p16^{INK4a}$ overexpressing neoplastic or dysplastic lesions in a uterine cervix sample in the course of cytological testing procedures. The discrimination method is based on the presence or absence of (a) cells expressing a high risk HPV gene-product and (b) cells overexpressing $p16^{INK4a}$ in the same uterine cervix sample.

The Response

35 USC §103(a) Rejection

Claims 1-3, 8, 11-17, 22-24 and 27 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Klaes et al. (2001, Int. J. Cancer 92:276-284) in view of Solomon et al. (2001, J. of the National Cancer Institute 93(4):293-299) and Guccione (Virology 293:20-25 (2002)), as evidenced by von Knebel Doeberitz (2001, Dis. Markers 17(3):123-8 (abstract only). The rejection is traversed because none of the prior art has disclosed a need to improve the specificity of p16 in a cytological testing procedure.

Klaes et al.

Klaes et al. report that "$p16^{INK4a}$ is a **specific** biomarker to identify dysplastic and neoplastic cervical epithelia in sections of cervical biopsy samples or cervical smears." (see last sentence of Abstract and Title). Klaes et al. do not describe any problems with the p16 staining when used in cytology. Klaes et al. do not recognize the problem that about 30% of metaplastic cases show some immunoreactivity with $p16^{INK4a}$ specific antibodies and that measuring $p16^{INK4a}$ alone cannot discriminate metaplasia from neoplasia in Pap smear.

The Examiner states that Applicant is arguing limitations not recited in the claims. Applicant respectfully disagrees. Claim 1 is directed to a method for discriminating $p16^{INK4a}$ overexpressing metaplasias from $p16^{INK4a}$ overexpressing neoplastic or dysplastic lesions in a uterine cervix sample in the course of cytological testing procedures, wherein the simultaneous presence of cells expressing the high risk HPV gene-product and cells overexpressing $p16^{INK4a}$

is indicative of neoplastic or dysplastic lesion, and the presence of cells overexpressing $p16^{INK4a}$ alone is indicative of metaplasias. Clearly, Klaes et al. failed to disclose the above-recited claim limitation.

A person skilled in the art reading Klaes et al. would understand that p16 is a sensitive and specific biomarker in the cytological testing and there is no need to search for another marker to improve the specificity of the test.

Solomon et al.

1. Solomon et al only disclose a test for HPV infection.

Solomon et al disclose testing HPV DNA (hc2) in solubilized cell samples, in women referred to colposcopy. Solomon et al. tested HPV DNA by solubilizing the cells; Solomon et al did not test HPV protein or use a cytological testing procedure. The hc2 test is a nucleic acid based test performed on lysed swab material, not on a cellular level. The hc2 test detects the nucleic acid of HPV, which indicates the infection with HPV. However, a high percentage of infection regresses and does not lead to oncogenic transformation. Therefore, the hc2 testing cannot discriminate metaplasic cells from dysplastic or neoplastic cells.

2. Solomon et al do not disclose testing cells expressing a high risk HPV gene-product.

After HPV infection, a high risk HPV gene-product such as E7 protein needs to be expressed in cells to induce and uphold oncogenic transformation. Solomon et al only disclose a test for the HPV infection, but do not disclose testing the E7 protein. As a matter of fact, at the time of this invention, there was no information on immunocytochemical testing of E7 in a uterine cervix sample.

3. A person skilled in the art would not have selected the combination of p16 with E7.

There is no hint in Solomon et al. that the HPV DNA testing should be combined with another testing of a different immunochemical marker. Even if there is any hint in Solomon et al, a person skilled in the art would not have selected the combination of p16 with E7 for the following reasons.

There are numerous markers for which immunohistochemistry testing on cervical lesions has been reported (claudin, p53, hTERT, Fhit, mcm2, cdc4, mcm5, p21, p27, c-Erb2,

Id1, bcl2, bax, integrin Alpha6, Muc2, Ki67, Cyclin E, Cyclin D1, Cyclooxigenase2, telomerese, E-cadherin, etc.). However, E7 was not reported for immunocytochemical testing in a uterine cervix sample prior to the present invention. There was no information on useful combinations in the art prior to the present invention.

The expression of the two proteins p16 and HPV E7 is closely interrelated. Von Knebel Doeberitz (*Dis Markers,* 17:123-8, 2001, cited by the Examiner) reports that "Expression of two viral oncogenes, E6 and E7, in epithelial stem cells is required to initiate and maintain cervical carcinogenesis and results in significant overexpression of the cellular $p16^{INK4a}$ protein." P16 is regarded as a cellular substitute marker to show oncogenic transformation with HPV E7. A person skilled in the art would have considered that the p16 and E7 markers are redundant, and that the combination of them would not render any additional information.

Guccione et al.

Guccione only teaches detection of recombinant HPV E7 protein that have been genetically modified to bear a haemagglutinin tag for enhanced detection. Guccione et al. do not mention $p16^{INK4a}$ at all or provide a method for discriminating p16 overexpressing metaplasias from p16 overexpressing neoplastic or dysplastic lesions. Guccione et al. do not cure the deficiency of Klaes et al. and Solomon et al.

Reduction to Practice

Klaes et al. identify $p16^{INK4a}$ as a specific biomarker. Klaes et al. do not recognize the false-positive problem of $p16^{INK4a}$ in metaplastic cells. Reading Klaes et al., a person skilled in the art would have no reason to combine another biochemical marker with $p16^{INK4a}$ to improve the specificity of the test, which discriminates metaplasia from dysplasia and neoplasia.

The cited references neither discovered the problem nor provided a solution to the problem. Applicants have discovered that two related biochemical markers of $p16^{INK4a}$ and the high risk HPV gene-product are not redundant and are complementary for discriminating metaplasias from neoplastic or dysplastic lesions. Applicants have reduced the invention to practice. In Example 1, cells originating from metaplasias were stained by the immunoreaction specific for p16, but not stained by the immunoreaction specific for the HPV E2 protein or HPV L1 protein; whereas dysplastic cells were stained by both p16 and E2/L1. In Example 3,

cells originating from metaplasias were stained by the immunoreaction specific for p16, but not stained by the immunoreaction specific for the HPV E7 protein; whereas neoplastic cells were stained by both p16 and E7.

Objections

Claims 2 and 8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 2 and 8 are cancelled.

Claim 23 is objected to because of an apparent typographical error. Claim 23 is amended according to the Examiner's suggestion.

Claim 27 is objected to because there appears to be text missing between "cells" and "high". Claim 27 is amended according to the Examiner's suggestion.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. Early notification of allowance is earnestly solicited.

Respectfully submitted,

Date: January 16, 2008

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Enclosure: Merriam Webster's Collegiate Dictionary, 10th Edition, 1997, page 731

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meta·phys·ic \ˌme-tə-ˈfi-zik\ *n* [ME *metaphesyk*, fr. ML *metaphysica*] (14c) **1** a : METAPHYSICS b : a particular system of metaphysics **2** : the system of principles underlying a particular study or subject : PHILOSOPHY 3b — **metaphysic** *adj*

meta·phys·i·cal \-ˈfi-zi-kəl\ *adj* (15c) **1** : of or relating to metaphysics **2** a : of or relating to the transcendent or to a reality beyond what is perceptible to the senses b : SUPERNATURAL **3** : highly abstract or abstruse; *also* : THEORETICAL **4** *often cap* : of or relating to poetry esp. of the early 17th century that is highly intellectual and philosophical and marked by unconventional imagery — **meta·phys·i·cal·ly** \-k(ə-)lē\ *adv*

Metaphysical *n* (1898) : a metaphysical poet of the 17th century

meta·phy·si·cian \ˌme-tə-fə-ˈzi-shən\ *n* (15c) : a student of or specialist in metaphysics

meta·phys·ics \-ˈfi-ziks\ *n pl but sing in constr* [ML *Metaphysica*, title of Aristotle's treatise on the subject, fr. Gk (*ta*) *meta* (*ta*) *physika*, lit., the (works) after the physical (works); fr. its position in his collected works] (1569) **1** a (1) : a division of philosophy that is concerned with the fundamental nature of reality and being and that includes ontology, cosmology, and often epistemology (2) : ONTOLOGY 2 b : abstract philosophical studies : a study of what is outside objective experience **2** : METAPHYSIC 2

meta·pla·sia \-ˈplā-zh(ē-)ə\ *n* [NL] (1890) **1** : transformation of one tissue into another **2** : abnormal replacement of cells of one type by cells of another — **meta·plas·tic** \-ˈplas-tik\ *adj*

meta·psy·chol·o·gy \-sī-ˈkä-lə-jē\ *n* [ISV] (ca. 1909) : speculative psychology concerned with postulating the structure (as the ego and id) and processes (as cathexis) of the mind which usu. cannot be demonstrated objectively — **meta·psy·cho·log·i·cal** \-ˌsī-kə-ˈlä-ji-kəl\ *adj*

meta·se·quoia \-si-ˈkwȯi-ə\ *n* [NL] (1948) : any of a genus (*Metasequoia*) of fossil and living deciduous coniferous trees of the bald cypress family that have leaves, buds, and branches arranged oppositely and flat leaves resembling needles

meta·so·ma·tism \-ˈsō-mə-ˌti-zəm\ *n* (1886) : metamorphism that involves changes in the chemical composition as well as in the texture of rock — **meta·so·mat·ic** \-sō-ˈma-tik\ *adj*

meta·sta·ble \-ˈstā-bəl\ *adj* [ISV] (1897) : having or characterized by only a slight margin of stability ⟨a ~ compound⟩ — **meta·sta·bil·i·ty** \-stə-ˈbi-lə-tē\ *n* — **meta·sta·bly** \-ˈstā-b(ə-)lē\ *adv*

me·tas·ta·sis \mə-ˈtas-tə-səs\ *n, pl* **-ta·ses** \-ˌsēz\ [NL, fr. LL, transition, fr. Gk, fr. *methistanai* to change, fr. *meta-* + *histanai* to set — more at STAND] (1663) : change of position, state, or form: as a : transfer of a disease-producing agency from the site of disease to another part of the body b : a secondary metastatic growth of a malignant tumor — **met·a·stat·ic** \ˌme-tə-ˈsta-tik\ *adj* — **met·a·stat·i·cal·ly** \-ti-k(ə-)lē\ *adv*

me·tas·ta·size \mə-ˈtas-tə-ˌsīz\ *vi* **-sized; -siz·ing** (1907) : to spread by or as if by metastasis

[1]**meta·tar·sal** \ˌme-tə-ˈtär-səl\ *adj* (1739) : of, relating to, or being the part of the human foot or of the hind foot in quadrupeds between the tarsus and the phalanges

[2]**metatarsal** *n* (1854) : a metatarsal bone

meta·tar·sus \ˌme-tə-ˈtär-səs\ *n* [NL] (1676) : the metatarsal part of a human foot or of a hind foot in quadrupeds

me·ta·te \mə-ˈtä-tē\ *n* [Sp, fr. Nahuatl *metlatl*] (1834) : a stone with a concave upper surface used as the lower millstone for grinding grains and esp. maize

me·tath·e·sis \mə-ˈta-thə-səs\ *n, pl* **-e·ses** \-ˌsēz\ [LL, fr. Gk, fr. *metatithenai* to transpose, fr. *meta-* + *tithenai* to place — more at DO] (1577) : a change of place or condition: as a : transposition of two phonemes in a word (as in the development of *crud* from *curd* or the pronunciation \ˈpür-tē\ for *pretty*) b : a chemical reaction in which different kinds of molecules exchange parts to form other kinds of molecules — **met·a·thet·i·cal** \ˌme-tə-ˈthe-ti-kəl\ *or* **met·a·thet·ic** \-tik\ *adj* — **met·a·thet·i·cal·ly** \-ti-k(ə-)lē\ *adv*

meta·tho·rac·ic \ˌme-tə-thə-ˈra-sik\ *adj* (ca. 1839) : of, relating to, or situated in or on the metathorax ⟨~ legs⟩

meta·tho·rax \-ˈthōr-ˌaks, -ˈthȯr-\ *n* [NL] (1816) : the posterior segment of the thorax of an insect — see INSECT illustration

meta·xy·lem \-ˈzī-ləm, -ˌlem\ *n* (1902) : the part of the primary xylem that differentiates after the protoxylem and that is distinguished typically by broader tracheids and vessels with pitted or reticulate walls

meta·zo·al \-ˈzō-əl\ *adj* [NL *Metazoa*] (1928) : of or relating to the metazoans

meta·zo·an \-ˈzō-ən\ *n* [NL *Metazoa*, fr. *meta-* + *-zoa*] (1884) : any of a group (*Metazoa*) that comprises all animals having the body composed of cells differentiated into tissues and organs and usu. a digestive cavity lined with specialized cells — **metazoan** *adj*

[1]**mete** \ˈmēt\ *vt* **met·ed; met·ing** [ME, fr. OE *metan*; akin to OHG *mezzan* to measure, L *modus* measure, Gk *medesthai* to be mindful of] (bef. 12c) **1** *archaic* : MEASURE **2** : to give out by measure : DOLE — usu. used with *out* ⟨~ out punishment⟩

[2]**mete** *n* [ME, fr. AF, fr. L *meta*] (15c) : BOUNDARY ⟨~s and bounds⟩

me·tem·psy·cho·sis \mə-ˌtem(p)-si-ˈkō-səs, ˌme-təm-ˌsī-\ *n* [LL, fr. Gk *metempsychōsis*, fr. *metempsychousthai* to undergo metempsychosis, fr. *meta-* + *empsychos* animate, fr. *en-* + *psychē* soul — more at PSYCH-] (1591) : the passing of the soul at death into another body either human or animal

met·en·ceph·a·lon \ˌmet-ˌen-ˈse-fə-ˌlän, -lən\ *n* [NL] (ca. 1871) : the anterior segment of the developing vertebrate hindbrain or the corresponding part of the adult brain composed of the cerebellum and pons — **met·en·ce·phal·ic** \-ˌen(t)-sə-ˈfa-lik\ *adj*

me·te·or \ˈmē-tē-ər, -ˌȯr\ *n* [ME, fr. MF *meteore*, fr. ML *meteorum*, fr. Gk *meteōron*, fr. neut. of *meteōros* high in air, fr. *meta-* + *-eōros*, fr. *aeirein* to lift] (15c) **1** : an atmospheric phenomenon (as lightning or a snowfall) **2** a : any of the small particles of matter in the solar system that are directly observable only by their incandescence from frictional heating on entry into the atmosphere b : the streak of light produced by the passage of a meteor

me·te·or·ic \ˌmē-tē-ˈȯr-ik, -ˈär-\ *adj* (1789) **1** : of, relating to, or derived from the earth's atmosphere ⟨~ water⟩ **2** a : of or relating to a meteor b : resembling a meteor in speed or in sudden and temporary brilliance ⟨a ~ rise to fame⟩ — **me·te·or·i·cal·ly** \-i-k(ə-)lē\ *adv*

me·te·or·ite \ˈmē-tē-ə-ˌrīt\ *n* (1824) : a meteor that reaches the surface of the earth without being completely vaporized — **me·te·or·it·ic** \ˌmē-tē-ə-ˈri-tik\ *also* **me·te·or·it·i·cal** \-ti-kəl\ *adj*

me·te·or·it·ics \ˌmē-tē-ə-ˈri-tiks\ *n pl but sing in constr* (ca. 1930) : a science that deals with meteors — **me·te·or·it·i·cist** \-ˈri-tə-sist\ *n*

me·te·or·oid \ˈmē-tē-ə-ˌrȯid\ *n* (1865) **1** : a meteor particle itself without relation to the phenomena it produces when entering the earth's atmosphere **2** : a meteor in orbit around the sun — **me·te·or·oi·dal** \ˌmē-tē-ə-ˈrȯi-dᵊl\ *adj*

me·te·o·rol·o·gy \ˌmē-tē-ə-ˈrä-lə-jē\ *n* [F or Gk; F *météorologie*, fr. MF, fr. Gk *meteōrologia*, fr. *meteōron* + *-logia* -logy] (1620) **1** : a science that deals with the atmosphere and its phenomena and esp. with weather and weather forecasting **2** : the atmospheric phenomena and weather of a region — **me·te·o·ro·log·ic** \-rə-ˈlä-jik\ or **me·te·o·ro·log·i·cal** \-ji-kəl\ *adj* — **me·te·o·ro·log·i·cal·ly** \-ji-k(ə-)lē\ *adv* — **me·te·o·rol·o·gist** \-ˈrä-lə-jist\ *n*

[1]**me·ter** \ˈmē-tər\ *n* [ME, fr. OE & MF; OE *mēter*, fr. L *metrum*, fr. Gk *metron* measure, meter; MF *metre*, fr. OF, fr. L *metrum* — more at MEASURE] (bef. 12c) **1** a : systematically arranged and measured rhythm in verse: (1) : rhythm that continuously repeats a single basic pattern ⟨iambic ~⟩ (2) : rhythm characterized by regular recurrence of a systematic arrangement of basic patterns in larger figures ⟨ballad ~⟩ b : a measure or unit of metrical verse — usu. used in combination ⟨penta*meter*⟩; compare FOOT 4 c : a fixed metrical pattern : verse form **2** : the basic recurrent rhythmical pattern of note values, accents, and beats per measure in music

[2]**met·er** \ˈmē-tər\ *n* [ME, fr. *meten* to mete] (14c) : one that measures; *esp* : an official measurer of commodities

[3]**me·ter** *n* [F *mètre*, fr. Gk *metron* measure] (1797) : the base unit of length in the International System of Units that is equal to the distance traveled by light in a vacuum in $^{1}/_{299,792,458}$ second or to about 39.37 inches — see METRIC SYSTEM table

[4]**me·ter** *n* [*-meter*] (1815) **1** : an instrument for measuring and sometimes recording the time or amount of something ⟨a parking ~⟩ ⟨a gas ~⟩ **2** : POSTAGE METER; *also* : a postal marking printed by a postage meter

[5]**me·ter** *vt* (1884) **1** : to measure by means of a meter **2** : to supply in a measured or regulated amount **3** : to print postal indicia on by means of a postage meter

-meter *n comb form* [F *-mètre*, fr. Gk *metron* measure] : instrument or means for measuring ⟨baro*meter*⟩

meter–kilogram–second *adj* (ca. 1940) : of, relating to, or being a system of units using the meter, kilogram, and second as its base units — abbr. *mks*

meter maid *n* (1957) : a woman assigned by a police or traffic department to write tickets for parking violations

me·ter·stick \ˈmē-tər-ˌstik\ *n* (1931) : a measuring stick one meter long that is marked off in centimeters and usu. millimeters

met·es·trus \ˌmet-ˈes-trəs\ *n* [NL] (1900) : the period of regression that follows estrus

meth- *or* **metho-** *comb form* [ISV, fr. *methyl*] : methyl ⟨*meth*acrylic⟩

meth·ac·ry·late \ˌme-ˈtha-krə-ˌlāt\ *n* [ISV] (1865) **1** : a salt or ester of methacrylic acid **2** : an acrylic resin or plastic made from a derivative of methacrylic acid

meth·acryl·ic acid \ˌme-thə-ˈkri-lik-\ *n* [ISV] (1865) : an acid $C_4H_6O_2$ used esp. in making acrylic resins or plastics

meth·a·done \ˈme-thə-ˌdōn\ *also* **meth·a·don** \-ˌdän\ *n* [*meth*yl + *amino* + *di*phenyl + *-one*] (1947) : a synthetic addictive narcotic drug $C_{21}H_{27}NO$ used esp. in the form of its hydrochloride for the relief of pain and as a substitute narcotic in the treatment of heroin addiction

meth·am·phet·amine \ˌme-tham-ˈfe-tə-ˌmēn, -thəm-, -mən\ *n* (1949) : an amine $C_{10}H_{15}N$ used medically in the form of its crystalline hydrochloride esp. in the treatment of obesity and often used illicitly as a stimulant — called also *methedrine*

metha·na·tion \ˌme-thə-ˈnā-shən\ *n* (1926) : the production of methane esp. from carbon monoxide and hydrogen

meth·ane \ˈme-ˌthān, *Brit usu* ˈmē-\ *n* [ISV] (ca. 1868) : a colorless odorless flammable gaseous hydrocarbon CH_4 that is a product of decomposition of organic matter and of the carbonization of coal, is used as a fuel and as a starting material in chemical synthesis, and is the simplest of the alkanes

meth·a·nol \ˈme-thə-ˌnȯl, -ˌnōl\ *n* [ISV] (1894) : a light volatile flammable poisonous liquid alcohol CH_3OH used esp. as a solvent, antifreeze, or denaturant for ethyl alcohol and in the synthesis of other chemicals

meth·aqua·lone \me-ˈtha-kwə-ˌlōn\ *n* [*meth-* + *-a-* (of unknown origin) + *qu*inoline + *azole* + *-one*] (1961) : a sedative and hypnotic nonbarbiturate drug $C_{16}H_{14}N_2O$ that is habit-forming — compare QUAALUDE

meth·e·drine \ˈme-thə-ˌdrēn, -drən\ *n* [fr. *Methedrine*, a trademark] (1939) : METHAMPHETAMINE

me·theg·lin \mə-ˈthe-glən\ *n* [W *meddyglyn*] (1533) : [1]MEAD

met·he·mo·glo·bin \ˌmet-ˈhē-mə-ˌglō-bən\ *n* [ISV] (1870) : a soluble brown crystalline basic blood pigment that differs from hemoglobin in containing ferric iron and in being unable to combine reversibly with molecular oxygen

met·he·mo·glo·bi·ne·mia \ˌmet-ˌhē-mə-ˌglō-bə-ˈnē-mē-ə\ *n* [NL] (1888) : the presence of methemoglobin in the blood

me·the·na·mine \mə-ˈthē-nə-ˌmēn, -mən\ *n* [*methene* (methylene) + *amine*] (1926) : hexamethylenetetramine esp. when used as a urinary antiseptic

meth·i·cil·lin \ˌme-thə-ˈsi-lən\ *n* [*meth-* + peni*cillin*] (1961) : a semisynthetic penicillin $C_{17}H_{19}N_2O_6NaS$ that is esp. effective against penicillinase-producing staphylococci

me·thinks \mi-ˈthiŋ(k)s\ *vb impersonal, past* **me·thought** \-ˈthȯt\ [ME *me thinketh*, fr. OE *mē thincth*, fr. *mē* (dat. of *ic* I) + *thincth* seems, fr. *thyncan* to seem — more at I, THINK] (bef. 12c) *archaic* : it seems to me

\ə\ abut \ᵊ\ kitten, F table \ər\ further \a\ ash \ā\ ace \ä\ mop, mar \au̇\ out \ch\ chin \e\ bet \ē\ easy \g\ go \i\ hit \ī\ ice \j\ job \ŋ\ sing \ō\ go \ȯ\ law \ȯi\ boy \th\ thin \t͟h\ the \ü\ loot \u̇\ foot \y\ yet \zh\ vision \à, ḵ, ⁿ, œ, ᵫ, ue, ue̅, ʸ\ see Guide to Pronunciation